8. In the preparation of a gel formulation which involves wet ball milling a calcipotriol component and adding the wet milled calcipotriol component to a gel base, the improvement which comprises wet milling calcipotriol hydrate as said component and using this wet milled hydrate for addition to said gel base.

REMARKS

Reconsideration is requested.

Claim 1 has been amended to obviate the Examiner's Section 112 rejection.

The dependence of claim 5 has been corrected and new claims 6-8 have been added for consideration.

Basis for the new claims is found throughout the applicants' disclosure. See, for example, the paragraph bridging pages 1-2 and the following two paragraphs on page 2 for claim 6; the 5th full paragraph, page 2 for claim 7; and Examples 5 and 6 for claim 8.

Claim 6-8 are thought to be allowable over the prior art for the same reasons as claims 1-5 noted hereinafter.

Reconsideration of the Section 103 rejection of claims 1-5 as unpatentable over Calverley et al. ('048) in view of Jolly et al. ('325) is requested. The references do not make the applicants' invention obvious.

As the applicants' specification indicates, calcipotriol is very useful for the topical treatment of psoriasis. It is desirable to formulate the calcipotriol in crystal form. To do this, the calcipotriol is usually subjected to a wet ball milling process in order to reduce the crystal size before the final suspension formulation is prepared. However, it has been found difficult to do this with the previously known form of

calcipotriol crystals. In particular, these crystals are not easily wetted and during the milling process they form a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

The applicants have surprisingly found that the problems previously encountered with calcipotriol can be avoided by their invention of the previously unknown crystalline calcipotriol hydrate. This hydrate has been found to be easily wetted, readily wet ball milled and surprisingly stable at 40°C. This stability is to be contrasted with the available anhydrous form of calcipotriol which shows considerable decomposition at 40°C, e.g., more than 30% degradation after 12 months' storage. This is to be compared with no degradation after 12 months storage at 40°C for the applicants' crystalline hydrate.

The Examiner's references do not in any way disclose or suggest the applicants' hydrate or its advantages. According to the Examiner Jolly et al. teaches "that the hydrated form of 1α,25-dihydroxycholecalciferol increases stability". However, the applicants do not agree with the Examiner's statement. Jolly mentions in passing that the monohydrate of 1α,25-dihydroxycholecalciferol is "very stable" but this does not teach anything about the stability of other forms of the compound, nor does it define what is meant by the term "very stable". Thus, one having ordinary skill in the art, reading Jolly, would not be taught that the crystalline monohydrate of 1α, 25-dihydroxycholecalciferol would be more stable than the crystalline anhydrous form of the same compound. For all the reference teaches, the stability of the two forms might be the same. Clearly, in the circumstances, one could not deduce from the prior art that the applicants' different crystalline monohydrate of calcipotriol would be more stable than the crystalline anhydrous form of calcipotriol, the latter being known from Calverley et al, 4,866,048. This

alone should be enough to establish unobviousness in the applicants' monohydrate.

Furthermore, apart from stability, the applicants' monohydrate of calcipotriol has other important technical properties which are unexpectedly superior to those of calcipotriol. These technical properties were crucial in the development of the commercial cream formulation which was launched in the US as Dovonex Cream by October 1996. Because cream formulations in which the active compound was dissolved were unstable, it was necessary to develop a crystal suspension formulation. However, as noted above, the crystalline anhydrous form of the drug gave rise to technical problems (such as wetting difficulties and foam formation) during the wet ball milling process. These technical problems have been successfully overcome by using the crystalline monohydrate of this invention.

Clearly there is nothing in either of the Examiner's references which suggests that the applicants' novel monohydrate would have the unique and unexpected properties discovered by the applicants. In the circumstances, it is urged that the Examiner's Section 103 rejection should be withdrawn and the claims allowed.

Favorable action is requested.

Respectfully submitted,

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